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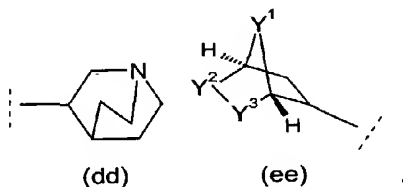
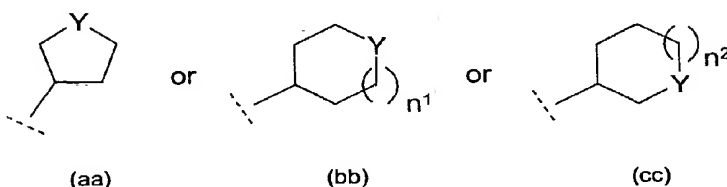
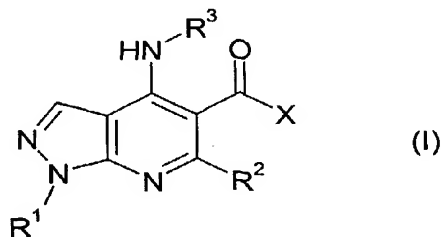
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[Continued on next page]

(54) Title: PYRAZOLO[3,4-B]PYRIDINE COMPOUNDS, AND THEIR USE AS PHOSPHODIESTERASE INHIBITORS



(57) Abstract: The invention relates to a compound of formula (I) or a salt thereof: wherein: R1 is C1-4alkyl, C1-3fluoroalkyl, -CH2CH2OH or -CH2CH2CO2C1-2alkyl; R2 is a hydrogen atom (H), methyl or C1fluoroalkyl; R3 is optionally substituted C3-8cycloalkyl or optionally substituted mono-unsaturated-C5-7cycloalkenyl or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc); in which n1 and n2 independently are 1 or 2; and in which Y is O, S, SO2, or NR10; or R3 is a bicyclic group (dd) or (ee); and wherein X is NR4R5 or OR5a. The compounds are phosphodiesterase (PDE) inhibitors, in particular PDE4 inhibitors. Also provided is the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal such as a human, for example chronic obstructive pulmonary disease (COPD), asthma, or allergic rhinitis.



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GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/11814

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 A61K31/437 A61P29/00 A61P11/00  
 //(C07D471/04,231:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 00 15222 A (SQUIBB BRISTOL MYERS CO)            23 March 2000 (2000-03-23)            claims 1,9</p> <p style="text-align: center;">--- -/--</p>	1,56,61



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

19 February 2004

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03/03/2004

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## INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; DALY, JOHN W. ET AL: "1-Methyl-4-substituted-1H-pyrazolo'3,4-b! pyridine-5-carboxylic acid derivatives: effect of structural alterations on activity at A1 and A2 adenosine receptors" retrieved from STN Database accession no. 122:45666 XP002270929 cited in the application abstract &amp; MEDICINAL CHEMISTRY RESEARCH (1994), 4(5), 293-306 ,  -----</p>	1,56,61

# INTERNATIONAL SEARCH REPORT

national application No.  
PCT/EP 03/11814

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 62 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/11814

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0015222	A	23-03-2000	AU 751486 B2	15-08-2002
			AU 6143899 A	03-04-2000
			CA 2342583 A1	23-03-2000
			EP 1113796 A1	11-07-2001
			JP 2002524512 T	06-08-2002
			WO 0015222 A1	23-03-2000
			US 6326379 B1	04-12-2001
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